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Translation

PATENT COOPERATION TREATY

PCT Application
PCT/JP2003/00

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 3043WO0P	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP2003/005172	International filing date (*day/month/year*) 23 April 2003 (23.04.2003)	Priority date (*day/month/year*) 24 April 2002 (24.04.2002)
International Patent Classification (IPC) or national classification and IPC A61K31/445, 31/4545, 31/351, 45/00, A61P1/00, 1/04, 1/14, 1/16, 1/18, 3/04, 3/10, 5/00, 7/00, 7/02, 7/10, 9/00, 9/04, 9/06, 9/10, 9/14, 11/00, 11/02, 11/06, 13/08, 13/10, 13/12, 15/00, 15/08, A61P17/00, 17/06, 19/00, 19/02, 19/10, 21/04, 25/00, 25/02, 25/04, 25/08, 25/14, 25/16, 25/18, 25/22, 25/24, 25/28, 25/32, 27/06, 27/14, 27/16, 29/00, 31/06, 31/10, 31/12, 31/16, 31/18, 31/22, 35/00, 35/02, 35/04, 37/00, 37/06, 37/08, 39/00, 41/00, 43/00, C07D211/14, 211/66, 211/96, 309/14		
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 15 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 20 May 2003 (20.05.2003)	Date of completion of this report 19 November 2003 (19.11.2003)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP2003/005172

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☐ the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:

pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. See supplemental sheet

because:

☒ the said international application, or the said claims Nos. 6
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See supplemental sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. See supplemental sheet .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III. 1.

[No examination has been made of the novelty, inventive step or industrial applicability of the inventions disclosed in the following claims, for the reason below.]

No international search report has been prepared for claims 1, 4, 5 and 7, except in as far as they refer to prophylactic or therapeutic agents for graft versus host disease and/or rejection reactions during organ transplants or bone grafts, characterized in that they contain a compound which has a CCR antagonist action and is represented by formula (eI), or a salt thereof.

Claim 6 pertains to methods for treatment of the human body by therapy, and thus relates to subject matter which does not require international preliminary examination by this International Preliminary Examining Authority.

Claims 1, 4, 5 and 7, except in as far as they refer to prophylactic or therapeutic agents for graft versus host disease and/or rejection reactions during organ transplants or bone grafts, characterized in that they contain a compound which has a CCR antagonist action and is represented by formula (eI), or a salt thereof

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

See supplemental sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. See supplemental sheet .

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

3.

Claims 1-5, 7 and 8 have in common the fact that they set forth compounds having a CCR antagonist action. However, results of the search have shown that compounds having a CCR antagonist action are not novel, because they are disclosed in documents WO, 99/32100 A1, WO 00/10965 A1, WO 00/37455 A1, WO 00/68203 A1, WO 00/76993 A1, WO 00/66551 A1, WO 01/25200 A1, WO 01/25199 A1, WO 00/66558 A1, WO 00/66559 A1, WO 01/42208 A1 and WO 01/64213 A1. As a result, compounds having a CCR antagonist action do not make a contribution over the prior art and, therefore, this common feature (compounds having a CCR antagonist action) is not a special technical feature un the sense of the second sentence of PCT Rule 13.2.

There is therefore no feature shared by all of the claims.

Since there is no other common feature that could be considered a special technical feature in the sense of the second sentence of PCT Rule 13.2, there is no technical relationship among these different inventions in the sense of PCT Rule 13.

Therefore, the inventions set forth in claims 1-5, 7 and 8 clearly do not satisfy the requirement of unity of invention.

Similarly, prophylactic or therapeutic agents for graft versus host disease and/or rejection reactions during organ transplants or bone grafts, and prophylactic

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

or therapeutic agents for rheumatoid arthritis, autoimmune disorders, allergies, ischaemic brain cell injury, myocardial infarction, chronic nephritis or arteriosclerosis containing a compound which has a CCR antagonist action are also clearly not novel, because they are disclosed in documents WO 00/66558 A1, WO 00/66559 A1, WO 01/42208 A and WO 01/64213 A1.

1) In as far as they refer to prophylactic or therapeutic agents for graft versus host disease and/or rejection reactions during organ transplants or bone grafts containing a compound which has a CCR antagonist action and is represented by formula (I), the technical feature of claims 1, 3, 5 and 7 is the use of a compound which has a CCR antagonist action and is represented by formula (I) for graft versus host disease and/or rejection reactions during organ transplants or bone grafts.

2) In as far as they refer to prophylactic or therapeutic agents for graft versus host disease and/or rejection reactions during organ transplants or bone grafts containing a compound which has a CCR antagonist action and is represented by formula (II), the technical feature of claims 1, 3, 5 and 7 is the use of a compound which has a CCR antagonist action and is represented by formula (II) for graft versus host disease and/or rejection reactions during organ transplants or bone grafts.

3) In as far as they refer to prophylactic or

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

therapeutic agents for graft versus host disease and/or rejection reactions during organ transplants or bone grafts containing a compound which has a CCR antagonist action and is represented by formula (III), the technical feature of claims 1, 3, 5 and 7 is the use of a compound which has a CCR antagonist action and is represented by formula (III) for graft versus host disease and/or rejection reactions during organ transplants or bone grafts.

4) In as far as they refer to prophylactic or therapeutic agents for graft versus host disease and/or rejection reactions during organ transplants or bone grafts containing a compound which has a CCR antagonist action and is represented by formula (IV), the technical feature of claims 1, 3, 5 and 7 is the use of a compound which has a CCR antagonist action and is represented by formula (IV) for graft versus host disease and/or rejection reactions during organ transplants or bone grafts.

5) In as far as they refer to prophylactic or therapeutic agents for graft versus host disease and/or rejection reactions during organ transplants or bone grafts containing a compound which has a CCR antagonist action and is represented by formula (eI), the technical feature of claims 1, 4, 5 and 7 is the use of a compound which has a CCR antagonist action and is represented by formula (eI) for graft versus host disease and/or rejection reactions during organ transplants or bone grafts.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

6) In as far as they refer to prophylactic or therapeutic agents for rheumatoid arthritis, autoimmune disorders, allergies, ischaemic brain cell injury, myocardial infarction, chronic nephritis or arteriosclerosis containing a compound which has a CCR antagonist action and is represented by formula (I), the technical feature of claims 2, 3 and 8 is the use of a compound which has a CCR antagonist action and is represented by formula (I) for rheumatoid arthritis, autoimmune disorders, allergies, ischaemic brain cell injury, myocardial infarction, chronic nephritis or arteriosclerosis.

7) In as far as they refer to prophylactic or therapeutic agents for rheumatoid arthritis, autoimmune disorders, allergies, ischaemic brain cell injury, myocardial infarction, chronic nephritis or arteriosclerosis containing a compound which has a CCR antagonist action and is represented by formula (II), the technical feature of claims 2, 3 and 8 is the use of a compound which has a CCR antagonist action and is represented by formula (II) for rheumatoid arthritis, autoimmune disorders, allergies, ischaemic brain cell injury, myocardial infarction, chronic nephritis or arteriosclerosis.

8) In as far as they refer to prophylactic or therapeutic agents for rheumatoid arthritis, autoimmune disorders, allergies, ischaemic brain cell injury, myocardial infarction, chronic nephritis or

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

arteriosclerosis containing a compound which has a CCR antagonist action and is represented by formula (III), the technical feature of claims 2, 3 and 8 is the use of a compound which has a CCR antagonist action and is represented by formula (III) for rheumatoid arthritis, autoimmune disorders, allergies, ischaemic brain cell injury, myocardial infarction, chronic nephritis or arteriosclerosis.

9) In as far as they refer to prophylactic or therapeutic agents for rheumatoid arthritis, autoimmune disorders, allergies, ischaemic brain cell injury, myocardial infarction, chronic nephritis or arteriosclerosis containing a compound which has a CCR antagonist action and is represented by formula (IV), the technical feature of claims 2, 3 and 8 is the use of a compound which has a CCR antagonist action and is represented by formula (IV) for rheumatoid arthritis, autoimmune disorders, allergies, ischaemic brain cell injury, myocardial infarction, chronic nephritis or arteriosclerosis.

10) In as far as they refer to prophylactic or therapeutic agents for rheumatoid arthritis, autoimmune disorders, allergies, ischaemic brain cell injury, myocardial infarction, chronic nephritis or arteriosclerosis containing a compound which has a CCR antagonist action and is represented by formula (eI), the technical feature of claims 2, 4 and 8 is the use of a compound which has a CCR antagonist action and is represented by formula (eI) for rheumatoid arthritis,

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

autoimmune disorders, allergies, ischaemic brain cell injury, myocardial infarction, chronic nephritis or arteriosclerosis.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.4

Claims 1, 4, 5 and 7 in as far as they refer to prophylactic or therapeutic agents for graft versus host disease and/or rejection reactions during organ transplants or bone grafts, characterized in that they contain a compound which has a CCR antagonist action and is represented by formula (eI), or a salt thereof

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims		YES
	Claims	1, 4, 5, 7	NO
Inventive step (IS)	Claims		YES
	Claims	1, 4, 5, 7	NO
Industrial applicability (IA)	Claims	1, 4, 5, 7	YES
	Claims		NO

2. Citations and explanations

Document 1: WO 99/32468 A1
Document 2: EP 1182195 A1
Document 3: WO 99/32100 A2
Document 4: WO 00/37455 A1
Document 5: EP 1186604 A1
Document 6: WO 00/66558 A1
Document 7: WO 00/66559 A1

Claims 1, 4, 5 and 7 are not novel and do not involve an inventive step in the light of document 1, cited in the international search report. Document 1 (claims and page 2) discloses compounds represented by formula (eI), and claims that said compounds are antagonists of the receptor for MCP-1, which belongs to the CC chemokine subfamily, and that they can be used for rejection reactions after organ transplantation, etc.

Claims 1, 4, 5 and 7 do not involve an inventive step in the light of documents 2-7, cited in the international search report. Documents 2-5 in their entirety disclose compounds represented by formula (eI), and also claim that said compounds have a CCR antagonist action; however, claims 1, 4, 5 and 7 relate to use of said compounds for rejection reactions during organ

transplantation, etc.; and this is not mentioned in documents 2-5. However, documents 6 and 7 disclose use of compounds which have a CCR antagonist action for rejection reactions during organ transplantation, etc. Therefore, given the disclosures in documents 6 and 7, a person skilled in the art could easily use compounds disclosed in documents 2-5, which have a CCR antagonist action and are represented by formula (eI), for rejection reactions during organ transplantation, etc.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
JP 2003-119191 A	23 April 2003 (23.04.2003)	07 August 2002 (07.08.2002)	08 August 2001 (08.08.2001)
[EX]			

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*